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Screening and Management of Atherosclerotic Cardiovascular Disease in Inflammatory Arthritis: A Comprehensive Approach for the Rheumatologist

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Inflammatory arthritis (IA) is associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD) and contributes to significant morbidity and mortality. Early identification and treatment of conventional cardiovascular disease (CVD) risk factors are pivotal in mitigating ASCVD risk among the IA population. Equally crucial is the proactive management of inflammatory disease, necessitating a thorough discussion of the risks and benefits, particularly regarding the use of some advanced therapeutic agents indicated for IA, which may carry an increased risk of CVD in high-risk subgroups.

This article reviews the current evidence for optimal CVD screening in IA. We underscore the importance of a holistic approach that incorporates conventional risk assessment tools, biomarkers, imaging techniques, and interdisciplinary cooperation.

Section 1: The Scope of the Problem—Epidemiology, Mechanisms, and Gaps in Conventional Cardiovascular Disease Care

Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) are the most common types of inflammatory arthritis (IA), affecting up to 5% of Canadians. The use of highly effective disease-modifying antirheumatic drugs (DMARDs), especially when administered early and aggressively, can effectively curb inflammation, safeguard against joint damage, and prevent disability. However, IA conditions are not confined to causing joint inflammation, and their systemic nature can extend to other organ systems, including the cardiovascular system. This involvement encompasses various cardiovascular diseases, including arrhythmias, valvular disease, pericarditis, myocarditis, and heart failure. Notably, epidemiological research reveals a 1.5- to 2-fold increased risk of incident atherosclerotic cardiovascular disease (ASCVD) events in

those with IA when compared to the general population, and CVD-related death continues to be the primary cause of premature mortality in IA patients.¹

This heightened risk of ASCVD in IA stems from the pathophysiological mechanisms intertwining inflammation and vascular dysfunction. The inflammatory hypothesis of ASCVD underscores the role of chronic inflammation as a pivotal player in atherogenesis, promoting endothelial dysfunction, plaque formation, and eventually plaque rupture, leading to total arterial occlusion. Inflammatory cytokines, such as tumour necrosis factor- α (TNF- α) and interleukin-6 (IL-6), contribute to systemic inflammation and accelerate atherosclerosis progression.²

Patients with poorly controlled IA, or those who have experienced a long disease duration with several episodes of active disease, are at a high risk for adverse CVD outcomes. In addition, factors such as male sex, older age, elevated inflammatory marker levels, and erosive disease are predictors of accelerated CVD.¹ For RA

specifically, factors such as high titre rheumatoid factor or anti-citrullinated peptide antibody (ACPA) and the presence of extra-articular manifestations are also associated with a higher risk of ASCVD.³ Studies exploring the contribution of IA characteristics suggest that up to 30% of the ASCVD risk may be attributed to disease specific variables and may be modified with aggressive treatment of the underlying IA.⁴ However, this highlights the point that most of the ASCVD risk stems from non-IA factors. Traditional CVD risk factors, including hypertension, dyslipidemia, cigarette smoking, and diabetes have increased prevalence in patients with IA. Patients with PsA and AS are more frequently male and have a higher burden of metabolic syndrome than patients with RA.⁴ These same metabolic risk factors are frequently underdiagnosed and undertreated in individuals with IA, further exacerbating their cardiovascular vulnerability. A number of barriers to optimal screening and control of metabolic risk factors have been identified.⁵ Patients with IA often receive focused care primarily targeting their joint symptoms, leading to inadequate attention to their CVD risk factors. Additionally, symptoms of IA may overshadow other comorbidities, leading to an under-recognition and underestimation of their significance. Furthermore, rheumatology providers may lack comfort in determining the best screening modalities to use, and they may also lack the time and resources to serially screen IA patients for metabolic conditions. Rheumatologists may also not be equipped to medically manage these comorbidities or provide advice on lifestyle. Additionally, there is the issue of potentially encroaching on each other's roles, and it remains uncertain whether this task should fall under the purview of the primary care physician, other health care providers, or the rheumatologist.⁶ Thus, the synergistic effect of systemic inflammation and suboptimal management of traditional risk factors increases the ASCVD risk, which emphasizes the importance of a comprehensive CVD risk assessment and management strategies in this high-risk population.

Section 2: Improving CVD Screening—Who? When? and How?

Several publications support enhanced CVD screening in patients with IA. First, they recognize that IA represents an above average at-risk population, with some suggesting that IA be considered a CVD risk-equivalent akin to diabetes.⁷ Second, the majority of guidelines support that the rheumatologist (despite some of the barriers cited above) has a central role in the evaluation of CVD risk.

One of the earliest recommendations came from the European League Against Rheumatism (EULAR). In 2009, EULAR formulated 10 recommendations for CVD risk management in patients with chronic inflammatory rheumatic diseases.⁸ This guideline recommends a risk assessment for CVD in all patients with systemic autoimmune rheumatic diseases, including IA, at least once every 5 years, and reconsideration after major changes to their DMARD therapy.⁸ If the patient is found to be at low risk after the initial screening, then a 5-year routine risk assessment is reasonable, unless there is a significant change in clinical status. If the initial screening puts the patient in a low-intermediate or intermediate risk category, then an earlier reassessment of risk may be considered. For those patients who are found to be at a high CVD risk based on the initial evaluation, institution of specific treatments to lower the ASCVD risk such as statin therapy or antihypertensive therapy would be indicated, along with follow up as needed to ensure targets of therapy have been reached.⁸

However, accurate ASCVD risk stratification in patients with IA can be challenging. The commonly used ASCVD risk calculators such as the Framingham Risk Score (FRS) including a [Canadian calculator](#), the Systematic Coronary Risk Evaluation ([SCORE](#)), and the American College of Cardiology/American Heart Association (ACC/AHA) [ASCVD Risk Calculator](#) provide a snapshot assessment incorporating various traditional risk factors including age, sex, smoking status, blood pressure, lipid profile, and diabetes.⁹ The benefits of these tools include familiarity, as many healthcare providers (particularly primary care) have these tools integrated into their electronic medical records. In addition,

they involve simple calculations based on readily available patient data. These tools also provide a systematic method to stratify patients into different risk categories (low, moderate, and high), to aid in guiding treatment decisions for primary prevention interventions. However, when these tools are applied to IA, they may not accurately reflect the cumulative exposure to dynamic risk factors in patients with a chronic, remitting and relapsing condition, and most do not account for systemic inflammation or incorporate inflammatory markers. Furthermore, most of these tools have not been validated in populations with IA, which can lead to inaccurate risk estimations. Lastly, traditional risk assessment tools do not account for risk factors that behave paradoxically in the presence of inflammation. For example, lipid levels may appear falsely favourable in the inflammatory milieu but start rising with better control of the underlying inflammation, known as the so-called 'lipid paradox'. These lipid levels are best assessed when inflammation is well controlled.¹⁰

Efforts to include non-traditional risk factors, disease-specific parameters, multipliers, and biomarkers have not yet been as successful at improving risk estimates in this population.⁹ In the absence of validated disease-specific risk estimators, most societies continue to recommend the use of national guidelines for CVD risk estimation. The 2017 EULAR update recommended using a multiplication factor of 1.5 for all patients with RA, which is based on a consensus opinion.⁸ This is in contrast to the 2009 EULAR guidelines that had recommended a multiplication factor of 1.5 for patients with RA who met specific criteria, which included a longer disease duration >10 years, rheumatoid factor (RF)/ACPA positivity, and the presence of extra-articular manifestations. This recommendation was based on the concern that using the selective approach would underestimate the risk.^{8,11}

Despite these recommendations, multiple studies have demonstrated that using the general risk predictors often results in an underestimate and at times an overestimate of cardiovascular risk in IA, and that applying the multiplication factor does not significantly improve risk prediction.^{9,12,13} Newer approaches that incorporate non-invasive imaging of subclinical atherosclerosis such as coronary artery calcium (CAC) scoring show promise for a more accurate ASCVD risk stratification in individuals in whom the ASCVD risk level remains unclear.¹⁴ The presence of coronary calcifications on cardiac CT scans is a strong

predictor of ASCVD risk. Further, increases in CAC scores are directly proportional to increases in the risk of ASCVD. Generally, a CAC score >100 is an indication for intensive CV risk reduction. The use of other biomarkers, including the evaluation of Lipoprotein(a) [Lp(a)], an LDL-like atherogenic lipid molecule shown to be causally related to ASCVD, can be helpful in further stratifying patients into appropriate risk categories.¹⁴

There are currently no specific Canadian guidelines for CVD screening in IA. Nevertheless, a set of CVD quality indicators tailored for RA was developed by Barber *et al.* in collaboration with rheumatologists, cardiologists, and patient representatives.¹⁵ These include communicating the above-average risk for CVD in IA to primary care providers, conducting regular CVD risk assessments in the same patient over time, addressing modifiable risk factors such as smoking, obesity, hypertension, diabetes, and dyslipidemia, and promoting healthy lifestyle recommendations (**Table 1**).¹⁵ Notably, the guidelines also underscore the importance of minimizing corticosteroid and non-steroidal anti-inflammatory drug (NSAID) use, a consideration not typically addressed in conventional CVD primary prevention guidelines. A follow-up study that evaluated the ease of applying these quality indicators in clinical practice found several gaps in CVD care. The quality indicators that focused on screening for risk factors or formal CVD risk estimation showed a poor performance, but documentation for the intent to taper steroids/NSAIDs was universally high among rheumatologists.¹⁶ As expected, rheumatologists may feel more at ease managing IA, but may be less inclined to address or take action on conventional CVD risk factors. These findings highlight the necessity for quality improvement initiatives to close this gap, including enhanced coordination of care among rheumatology, primary care, and cardiology. Each specialty possesses unique expertise, and collaborative efforts are essential to ensure comprehensive and effective management.

Section 3: Management of Traditional CVD Risk Factors—What Rheumatologists Can Learn About Treatment Targets

The importance of a heart healthy lifestyle including total smoking cessation, adherence to a heart-healthy diet, weight management, and regular physical activity should be emphasized to

all patients. Providing a recommendation for total smoking cessation at every visit, and a referral to smoking cessation programs for individuals who feel ready to quit smoking should be considered at each clinical encounter. Adherence to a diet rich in vegetables, fruits, legumes, nuts, whole grains, and fish along with reduced amounts of dietary cholesterol, particularly saturated and trans fats, refined carbohydrates, and sodium is recommended to reduce ASCVD risk. The **Mediterranean diet** can improve both CV risks (cholesterol, blood pressure) and can also slightly improve inflammatory arthritis so it can be suggested to patients with IA and CVD risk factors.

Patients should engage in at least 150 minutes per week of moderate-intensity exercise, or 75 minutes per week of vigorous-intensity aerobic physical activity to reduce ASCVD risk.¹⁷ Achieving these physical activity targets can be particularly challenging for individuals with IA due to joint limitations; thus, activities such as swimming or other water-based sports, which are generally easier on the joints, should be considered.

The current EULAR recommendation for the management of individual CVD risk factors in IA, including hypertension and dyslipidemia, is to follow the recommendations set for the general population. For patients with dyslipidemia who are at a high ASCVD risk, the typical recommendation is to reduce LDL-cholesterol to <2.0 mmol/L in the primary prevention setting and to <1.8 mmol/L in the secondary prevention setting, with the use of optimal dosing of statins as first-line therapy (especially rosuvastatin or atorvastatin), and additional lipid lowering therapies as needed, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors.¹⁸ The specific targets of therapy for hypertension vary somewhat between different sets of guidelines set for the general population, however, in general, a target blood pressure of 130/80 mmHg is recommended for individuals at a high ASCVD risk. This target is usually achieved with the use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, or diuretics as typical first-line agents. Individuals who have diabetes as an additional risk factor should undergo careful evaluation with their primary care physician or endocrinologist to achieve the best possible glycemic control to prevent microvascular and macrovascular complications.

Section 4: The Role of DMARDs/Biologics in ASCVD Risk Reduction

DMARDs and biologics offer potential benefits beyond the joints and have been shown to lower ASCVD risk. However, achieving aggressive control of inflammation is imperative to unlock these cardioprotective effects. There is substantial evidence supporting the cardioprotective properties of methotrexate and TNF inhibitors (TNFi), which have been associated with a reduced risk of myocardial infarction, stroke, and heart failure (HF) development among patients with IA.¹⁹ Methotrexate and cytokine inhibitors have made headlines for their ability to lower the CVD risk, possibly even in non-rheumatic populations (for biologics such as IL-1i), by targeting the pivotal role that inflammation plays in CVD development.²⁰

In contrast, the use of NSAIDs can have undesirable CVD effects, including hypertension, myocardial infarction, stroke, and HF. Glucocorticoid use is similarly associated with a variety of adverse CVD effects including hypertension, fluid retention, premature atherosclerosis, myocardial infarction, arrhythmias, and HF. NSAIDs and glucocorticoids should be prescribed with extreme caution, especially for those with known CVD or multiple CVD risk factors. All guidelines, irrespective of patient age, recommend limiting the dose and duration to prevent CVD events and the multiple other adverse effects associated with these medications.^{8,15,21}

Furthermore, while certain biologics such as tocilizumab may lead to anticipated increases in lipid levels due to their mechanism of action, the interplay between lipids and inflammation in this scenario is intricate. During active disease states, lipid levels paradoxically tend to be low. Although lipid levels may rise as disease control improves, not all of this increase is driven by highly atherogenic particles. Indeed, biologics may have a favourable impact on “good cholesterol” by enhancing the structure and function of high-density lipoprotein (HDL), while concurrently reducing the levels of other “bad” CVD biomarkers such as serum amyloid A and Lp(a).²² Consequently, the timing of lipid assessment becomes critical, and is typically performed at baseline and then approximately 12 weeks after treatment initiation, or upon reaching a state of low disease activity. Should lipid levels remain elevated or concerning despite adequate disease

Recommendations		Comments
Traditional Risk Factor Screening and Management		
Perform CVD risk assessment	- Communicate regularly that IA is a risk factor for CVD with both the PCP and patient - The formal CVD risk assessment tool should be used at least once within the first 2 years of diagnosis - If low risk, repeat the risk assessment every 5 years - If intermediate risk or higher, treat the modifiable risk factors - Repeat the assessment any time there is a sustained change in disease activity	
Measure the lipid panel	- Recommended once within 2 years of diagnosis and then annually - Interpretation of lipid levels should be performed with caution when the disease is active, it is recommended to check lipid levels once the disease activity is low or ~12 weeks after DMARD initiation/changes - If lipid levels are abnormal, relay the results to the PCP for management or refer to the appropriate health care professional	
Screen for diabetes	Check HbA1C and fasting glucose levels once within 2 years of diagnosis and annually	
Measure blood pressure	- Record annually - Communicate abnormal blood pressure results (systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90) to primary care or refer to the appropriate health care professional - If repeated blood pressure assessments are high, treatment should be initiated, or current anti-hypertensive medications should be adjusted	
Perform CVD risk score	Perform annually or any time there is a change in the disease status	
Smoking	- Document smoking status annually - Smoking cessation should be encouraged at every visit - Explore smoking cessation options by liaising with primary care	
Weight	- Record body mass index and waist circumference annually - If overweight or obese, counsel on lifestyle interventions and communicate this with the PCP or appropriate health care professional	
Exercise	Benefits of physical activity and recommended Canadian guidelines for exercise should be discussed annually	

Recommendations	Comments
Management of IA Risk Factors	
Disease activity should be as low as possible	• Treatment should target low disease activity or remission in IA
Limit exposure to corticosteroids	• Discourage chronic use of corticosteroids and discuss the possible CVD risks with the patient • If needed for flares, use the lowest effective dose and for the shortest duration possible • Discuss the intent to taper corticosteroids if used long term
Limit exposure to NSAIDs	• Use NSAIDs at lowest effective dose and for the shortest duration possible • Discourage chronic use and discuss the possible CVD risks with the patient
Therapeutic DMARD Considerations	
The goal of DMARD therapy is to suppress systemic inflammation	• Use of csDMARDs (most evidence is in support of methotrexate) and bDMARD have overall net cardioprotective benefits
DMARD therapy may alter traditional CVD risk factors	• Be aware of the “lipid paradox” and optimal timing to check lipids and anticipated changes in the lipid profile pre- and post-treatment • No clear evidence that DMARD therapy independently increases the risk of diabetes or hypertension
A suitable therapeutic alternative to tsDMARD should be considered in patients with history or risk factors for ASCVD	• Consider for males, and for those aged >65 years
If no suitable treatment alternatives are available for a patient with high ASCVD risk, a JAKi can be considered	• Refer to cardiology for assessment ideally before starting JAKi to optimize reversible ASCVD risk factors and for ongoing monitoring as indicated

Table 1. Approach to ASCVD risk assessment and management in patients with IA; adapted from Barber et al¹⁵, and Avouac²¹ et al.

Abbreviations: **ASCVD:** atherosclerotic cardiovascular disease, **bDMARD:** biologic disease modifying antirheumatic drug, **csDMARD:** conventional synthetic disease modifying antirheumatic drug, **HbA1C:** hemoglobin A1C, **JAKi:** Janus kinase inhibitor, **PCP:** primary care physician, **NSAIDs:** nonsteroidal anti-inflammatory drugs, **tsDMARD:** targeted synthetic disease modifying antirheumatic drugs

control, adherence to national guidelines for dyslipidemia management is recommended over withholding potentially effective biologic therapy.¹⁸ Moreover, newer lipoprotein markers (Lp(a), Apolipoprotein B), are less susceptible to inflammation-induced fluctuations, and offer a more dependable means of CVD risk assessment in patients undergoing biologic treatment. However, interpretation and treatment based on these parameters likely warrants collaboration with a cardiologist or another experienced health care provider. Additionally, a head-to-head CVD outcomes trial in active RA patients failing MTX demonstrated that CV events were not different between etanercept (a TNFi) and tocilizumab.²³

The ORAL Surveillance study sparked significant controversy regarding the safety of Janus kinase inhibitors (JAKi). The study observed an increased number of major adverse CVD events (MACE) and malignancies in JAKi-treated patients compared to TNFi-treated patients over the age of 50 years with at least one CVD risk factor.²⁴ This finding substantially changed many rheumatology practices and prescribing patterns due to the implementation of warnings on all JAKi, and concerns of a potential “class effect”, despite the study being conducted only on tofacitinib.

A number of post-hoc analyses of the ORAL Surveillance study indicate an elevated MACE risk in RA patients with prior CVD events or multiple risk factors, which include males, older age (>65 years), and current smokers.^{25,26} In contrast, trials of baricitinib and upadacitinib have not shown a distinctly increased risk of MACE at the doses approved for RA treatment, compared to TNFi or placebo.²⁶ Real-world data suggests that this overall risk remains generally low, however, there are trends toward higher CVD event rates in patients who are similar to those included in the ORAL Surveillance study.

Overall, the risks from JAKi treatment are clearly influenced by the baseline CVD risk, and documentation of this risk can aid clinical decision making and counselling. This risk is also influenced by multiple factors, which include the following: the specific indication for using the JAK (disease severity, extra-articular manifestations), other known comorbidities, previous response to therapy, the availability of alternative treatments, the type and dose of the JAKi chosen, and other risk-benefit considerations, including the ability to minimize the use of NSAIDs and corticosteroids.²⁵ When faced with limited treatment options,

prioritizing effective inflammation control should be paramount, even in the face of potential risks associated with JAKi therapy. To address this challenge, we recommend implementing regular and focused screening when considering any IA treatment changes. Additionally, for high-risk patients, a proactive referral to a cardiologist for a comprehensive evaluation and management can ensure optimal CVD care alongside IA treatment strategies. Thus, personalized assessment and monitoring are crucial to optimize treatment outcomes while minimizing potential adverse effects with JAKi or any advanced therapeutic (Table 1).

Section 5: Interdisciplinary Collaboration: The Emergence of Cardio-Rheumatology

The emerging discipline of ‘Cardio-Rheumatology’ represents a collaborative multidisciplinary approach to addressing the complexities involved in the cardiovascular care of patients with underlying systemic inflammatory disease. Despite the high degree of awareness about this elevated risk among rheumatologists, a high percentage of patients with IA remain underdiagnosed and undertreated with regards to CVD risk factors, and a lack of care coordination has been identified by rheumatologists and primary care providers as a large barrier to optimized CVD risk management.²⁷ As such, a dedicated cardiac assessment of these patients with the use of advanced biomarkers and imaging modalities, including CAC scoring, can help with the early identification and treatment of CVD and associated risk factors. Knowledge about the effect of medications, including anti-inflammatory therapies, corticosteroids, and DMARDs, on the cardiovascular system is crucial. Cardiologists in these clinics review this aspect very carefully to ensure optimal patient care. For example, considering the CVD safety signals brought forward by the ORAL Surveillance trial, a more careful ASCVD risk stratification might be required for a subset of patients being considered for targeted synthetic disease-modifying antirheumatic drug (tsDMARD) therapy. This can inform risk/benefit discussions and potentially lead to more aggressive risk management approaches in those who require the use of such medications. A number of other benefits of coordinated care have been identified, including the importance of patient education and advancing research opportunities to include

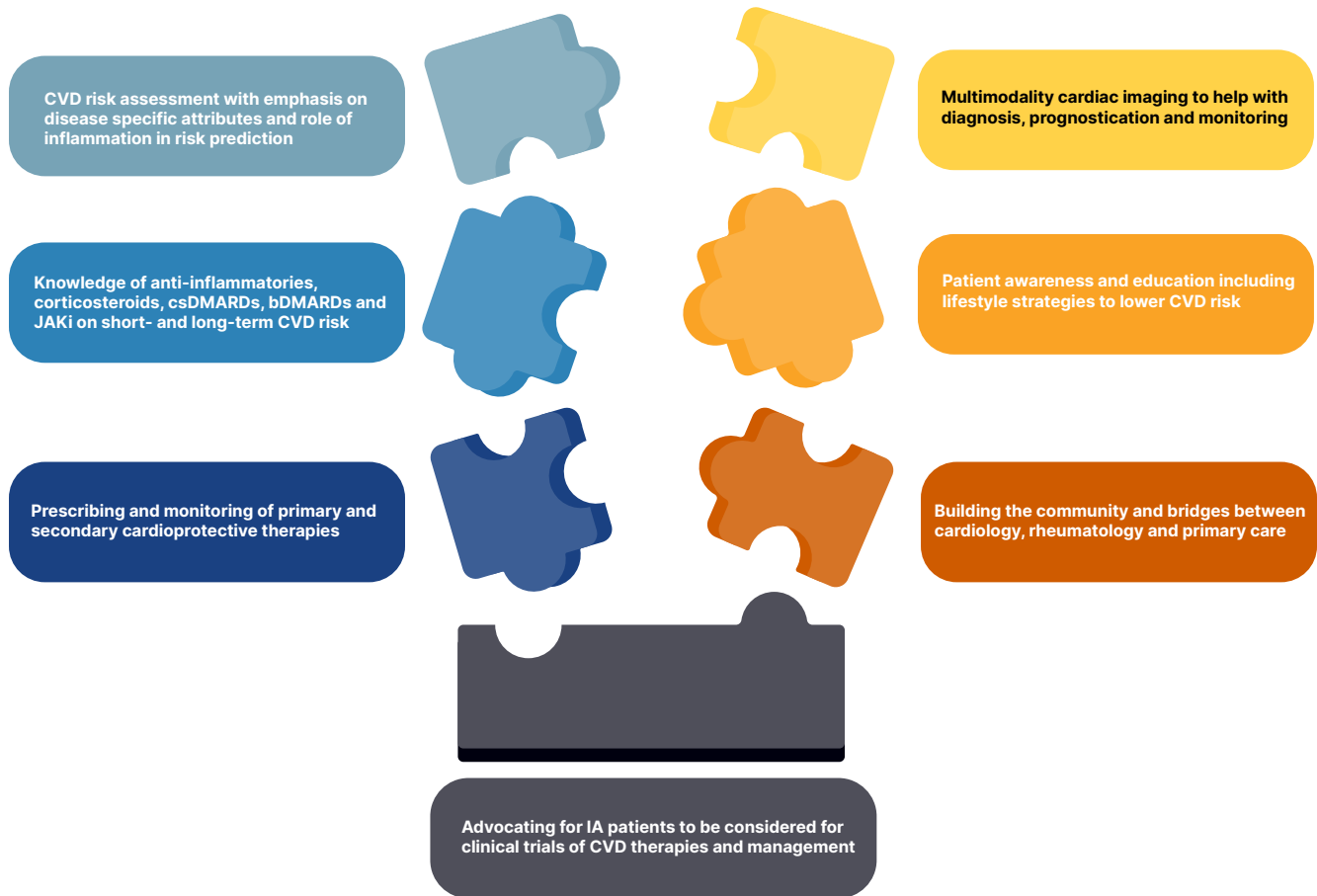


Figure 1. How cardio-rheumatology models of care can improve overall CVD risk stratification and management in IA; adapted from Weber *et al.*²⁹

this underrepresented population in clinical trials (**Figure 1**).

To date, a number of cardio-rheumatology clinics have emerged in Europe and North America. To our knowledge, the University of Toronto hosts the first and largest such program in Canada. Established in 2017, the program aims to improve primary CVD prevention for patients with IA. Close to 700 patients have undergone screening at this program which involves nurses, rheumatologists, cardiologists, and radiologists. Using newer lipoprotein parameters and coronary CT scans, we have significantly enhanced the risk

assessment in most patients. Notably, nearly half of asymptomatic IA patients have been identified as eligible for statin/lipid-lowering therapies according to Canadian dyslipidemia guidelines.²⁸ Moreover, this initiative boasts strong patient acceptance and relies on readily accessible tests and procedures that cardiologists can request and act upon. We view this as a scalable model that can be replicated in other centres and community hospitals and may help close the previously identified care gaps.

Conclusion

Patients with IA are at an increased risk of cardiovascular morbidity and mortality. Effective control of inflammation, careful cardiovascular screening, and aggressive management of cardiovascular risk factors are key in reducing this risk. A practical approach to helping assess and treat CVD risk factors in patients with IA is to document the risks and facilitate investigation and management by routinely adding the increased CV risk in your notes to the primary care physician and to treat the targets at least using a risk calculator and even considering the risks similar to type II diabetics and using established targets for HTN, hyperlipidemia and type 2 diabetes mellitus.

Cardio-Rheumatology, a multidisciplinary collaboration between rheumatologists and cardiologists, is crucial for the design and delivery of an integrated care plan that considers the intricacies involved in providing care to this complex patient population. Such collaborations can also help combine research efforts between the two disciplines and help fill current knowledge gaps and improve the quality of cardiovascular care offered to all patients living with rheumatic diseases.

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Financial Disclosures

B.K.: Advisory Board: AbbVie, Pfizer

S.A.: None declared.

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